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Anti-Nogo-A antibody: A treatment option for neurogenic lower urinary tract dysfunction?

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In the late 1980's, Caroni and Schwab (1) showed that the myelin membrane of oligodendrocytes is inhibiting nerve fiber growth in the central nervous system (CNS). A monoclonal IgM antibody against an unknown CNS myelin protein later known as Nogo-A induced substantial axonal sprouting and functional recovery in vitro and in vivo. Nowadays, the responsible neurite growth inhibitory surface protein Nogo-A and its receptors NgR1 and S1PR2 are identified and well-studied (2, 3). Nogo-A destabilizes the cytoskeleton via the rho/ROCK pathway causing growth cone collapse and inhibits neuronal growth and plasticity by down-regulation of growth-associated genes. Nogo-A suppression or neutralization leads to an increase in sprouting, axonal regeneration and neuronal plasticity and thereby to greater functional recovery after different types of CNS injuries.

In close collaboration with Novartis, a function blocking, high affinity human anti-human Nogo-A antibody (ATI355) was developed for intrathecal application. A clinical phase 1 study using this anti-Nogo-A antibody in acute, severe spinal cord injury patients was conducted by Novartis in several spinal cord injury centers in Europe and Canada. This phase 1 safety study has been recently completed successfully (http://clinicaltrials.gov/show/NCT00406016) and a placebo-controlled phase 2 "proof of concept study" is in preparation. In addition, based on very promising findings in animal studies (2, 4), trials assessing the effect of anti-Nogo-A in acute stroke and in amyotrophic lateral sclerosis (conducted by GSK) are in preparation or on-going (5). Importantly, anti-Nogo-A antibody treatment might also become an effective therapeutic option for neurogenic lower urinary tract dysfunction (NLUTD): Liebscher et al. (6) have found a significantly higher rate of corticospinal tract sprouting and regeneration after transection in adult rats when the animals were treated with function blocking antibodies against the neurite growth inhibitory protein Nogo-A as compared to control antibody treated rats (Figure). The treated animals reached significantly higher scores in a variety of sensory-motor tests and showed improved recovery of locomotion and motor coordination. During the first ten days after injury, the animals were not able to void and their bladders had to be emptied manually two to three times a day. In the control antibody treated group, voiding started to recover on average around 24 days after SCI. Remarkably, voiding was restored more than one week earlier in the anti-Nogo-A antibody treated rats (6).

Suppression of Nogo-A or its receptor NgR1 enhances neurite growth in the adult CNS (2, 7). In the injured CNS, regenerative and compensatory sprouting as well as

long distance regeneration of fibers in many parts of the spinal cord and brain are enhanced by functional blockade of Nogo-A signaling(2). These processes probably lead to new connections and functional circuits, for example from the pontine micturition center to the sacral micturition neurons, directly or via long proprio-spinal interneurons. In addition, anti-Nogo-A antibodies could induce plasticity in the circuits of the pontine and sacral micturition centers causing reorganization.

To elucidate the mechanisms of action and the potential of anti-Nogo-A antibody therapy for treating NLUTD, animal studies with detailed urodynamic measurements in different neuronal disease models causing NLUTD are currently ongoing. In addition, urodynamic investigations are planned to assess lower urinary tract function in the coming clinical studies. Future animal and human studies will show if anti-Nogo-A antibody treatment has the potential to improve our management of NLUTD.

Conflicts of Interest: None disclosed.

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Figure: Spinal cord injured rats were treated with two different IgG anti-Nogo-A antibodies (11C7 and 7B12). Reconstructions of the spinal hemicord with labeled corticospinal tract (CST), lesion site (light area), rostral (left side) sprouting zone, and CST fibers regenerating over tissue bridges (gray-shaded depiction) into the caudal spinal cord (right side). In both anti-Nogo-A antibody treated groups (11C7 and 7B12) were substantially more CST fibers regenerating (dark fibers on the right side of the lesion) compared to control IgG antibody treated animals. The anti-Nogo-A antibody treated animals had higher scores in sensory-motor tests and showed improved recovery of independent bladder voiding, locomotion and motor coordination.- **From Ref. (6**_ENREF_1**) with permission.**